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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/506,011	02/17/2000	John Cooper Cox	017227/0155	6856

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EXAMINER
FOLEY, SHANON A

ART UNIT	PAPER NUMBER
1648	

DATE MAILED: 02/25/2003

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/506,011	COX ET AL.	
	Examiner	Art Unit	
	Shanon Foley	1648	

-- Th MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 August 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-17* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

In paper no. 21, applicant canceled claims 18-43, 52 and amended claims 1-17.

Sequence Compliance

The specification is objected to for failing to adhere to the requirements of the sequence rules. Applicant must append SEQ ID Nos. to all mentions of specific sequences in the specification, see page 36, line 6 for example. See 37 CFR § 1.821 (a)-(d) and MPEP § 2422.

Specification

In paper no. 28, applicant provided a clean version of the specification. The disclosure is objected to because of the following informalities:

It cannot be determined what changes, if any, have been incorporated into the proposed disclosure. Applicant has not indicated which changes have been amended and has not provided a statement assuring that no new matter has been presented. In addition, no marked-up version of the specification was provided. Therefore, the clean version of the specification submitted 10/15/02 has been placed in the file wrapper, but has not been officially entered.

Claim Objections

Claim 17 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim 1. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 1 is drawn to a complex generating a CTL response when administered to an animal and claim 17 is drawn to the same complex inducing a cytotoxic T-lymphocyte response. Therefore, the concept presented in claim 17 fails to further limit the subject matter of claim 1.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-17 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is drawn to a "complex" comprising a negatively-charged organic "complex". It is unclear if there is a difference between each complex or what each comprises. This rejection also affects claims 2-17.

Claims 3-5 are drawn to a "derivative or equivalent" of a protein and an adjuvant. There is no definition provided for what these components encompass and the metes and bounds for what is considered a "derivative or equivalent" of a protein and an adjuvant cannot be determined from page 15, lines 9-27. This rejection also affects claims 6-16 and could be obviated by deleting the phrase from the claims.

Claim 10 is vague and indefinite because it cannot be discerned what the difference between the claimed "saponin" of claim 9 and the "saponin complex" of claim 10 is. Although the specification on page 12, line 27 provides an example of a saponin complex, i.e. ISCOMATRIX™, there is no definition provided that clearly indicates the metes and bounds of the components intended within a "saponin complex".

Claim 11 contains the trademark/trade name ISCOMATRIX™. Where a trademark or trade name is used in a claim as a limitation to identify or describe a particular material or product, the claim does not comply with the requirements of 35 U.S.C. 112, second paragraph.

See *Ex parte Simpson*, 218 USPQ 1020 (Bd. App. 1982). The claim scope is uncertain since the trademark or trade name cannot be used properly to identify any particular material or product. A trademark or trade name is used to identify a source of goods, and not the goods themselves. Thus, a trademark or trade name does not identify or describe the goods associated with the trademark or trade name. In the present case, the trademark/trade name is used to identify/describe the saponin complex and, accordingly, the identification/description is indefinite.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-17 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

Claim 1 is drawn to a complex comprising a negatively-charged organic complex that is electrostatically associated with a charged antigen. On page 9, lines 14-15, the specification defines "complex" as two or more chemical components that interact with each other. The disclosure does not describe a feature that distinguishes between the complex and the organic complex. The claims also specify that the antigen is a protein or a "derivative or equivalent thereof'. However, the disclosure does not describe what is intended by a derivative or equivalent of a protein on page 10, lines 20-28. The claims are also drawn to a derivative or equivalent of an adjuvant. On page 12, lines 19-22, the specification defines adjuvant as any

substance that potentiates an immune response. Although there is functional language provided for what the adjuvant does, there is no structural definition. The claims do not require that the protein or adjuvant possess any particular distinguishing feature, biologic activity, or conserved structure, except for their respective overall charge. Therefore, since the individual positively-charged proteins and negatively-charged adjuvants and derivatives and equivalents thereof are drawn to a broad genus of components have not been adequately described in the specification, there is also a lack of written description provided for the electrostatic association of these undefined components within the claimed complex. The specification does not convey possession of all positively-charged proteins or negatively-charged adjuvants or derivatives or equivalents thereof, or the electrostatic association of these components in a complex.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In this case, the only factor present in the claim is a required charge for each of the two essential ingredients. There is not even identification of any particular portion of the structures that must be conserved for each of the components within the complex. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus of negatively-charged organic complexes, positively-charged proteins, derivatives, or equivalents, or the complexes comprising these components by electrostatic association.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemi chemical structure of the encompassed genus of complexes, negatively-charged adjuvants or positively-charged proteins, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Claims 1-8 and 17 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a negatively-charged specific adjuvants: saponins or phospholipids, electrostatically associated with positively-charged antigens to induce a CTL response, does not reasonably provide enablement for any negatively-charged organic molecule,

adjuvants or derivative or equivalent thereof electrostatically associated with any charged or positively-charged antigen or derivative or equivalent thereof to induce a CTL response The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

The scope of the claims encompasses any negatively-charged organic molecule electrostatically associated with any charged antigen or any positively-charged protein or derivative or equivalent thereof. The specification does not define what is intended by derivatives or equivalents of the instant adjuvants or proteins and the skilled artisan would be unable to determine the metes and bounds of the molecules claimed. This lack of written description for the instant compounds has been discussed above and is incorporated herein. The skilled artisan is unable to predict the structure or function of the instant organics and antigens claimed from the teachings in the specification. Therefore, the skilled worker would be unable to make the claimed complexes commensurate with the scope of the claims.

Further, the working examples only use adjuvants that are well known in the art to demonstrate a potentiation of a CTL response. There are no working examples illustrating complexes comprising other negatively-charged organics or antigens or derivatives of each component within the complex. The specification does not provide any guidance for how to electrostatically associate undescribed molecules that would induce a CTL response and the skilled artisan would be unable to predict whether a cytotoxic response would be elicited based on the charge of the ingredients within the complex. The data provided from the working examples indicate that an induction of a CTL response is directly proportional to the electrostatic association between a negatively charged adjuvant and a positively-charged antigen. Working

example 6 clearly indicates that the naturally negatively-charged E6/E7 protein does not induce a CTL response when the protein is associated with DPPC ISCOMATRIX™.

The teachings of Nakanishi et al. (Biochemical and Biophysical Research Communications. 1997; 240: 793-797) demonstrate the level of skill in the art. The overall charge of the lipid composition PA:PC:Chol in Table 1 of Nakanishi et al. is made negative by the addition of phophatidic acid to the lipid carrier. The method of making the negatively-charged lipid of Nakanishi et al. agrees with the teachings in the disclosure on page 13, lines 25-29. In applicant's response, applicant "assumes" that the pI values that would result in the antigen of Nakanishi et al. to have a negative charge. However, no such conclusions can be made from the data provided in the reference and claim 1 only requires that the antigen be charged. Therefore, due to the natural, positive charge of some amino acid residues within each of the antigens used in the reference, it is maintained that these residues are electrostatically associate with the negatively charged particles within the liposome. The negatively charged liposome of Nakanishi et al. comprises the ingredients required by the claims. As noted by applicant in the response, the reference teaches that the negatively-charged complex does not induce a CTL response. Therefore, since the complex of Nakanishi et al. clearly fall within the scope of the instant claim 1 and does not generate a CTL response, the teachings of Nakanishi et al. and the data provided in working example 6 clearly demonstrate that the scope of the claimed complexes are not enabled for generating a CTL response.

In conclusion, due to the scope of the claim comprising any negatively-charged organic complex and any charged antigen to induce a CTL response, the data provided in the working example indicating that negatively-charged antigens and negatively-charged adjuvants do not

induce a CTL response and the state of the art clearly demonstrating that the scope of the negatively-charged organics complexed to any antigen does not induce a CTL response, it is determined that the invention would require an undue amount of experimentation to practice the invention in its full scope.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) do not apply to the examination of this application as the application being examined was not (1) filed on or after November 29, 2000, or (2) voluntarily published under 35 U.S.C. 122(b). Therefore, this application is examined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claims 1-8 and 12-17 are rejected under 35 U.S.C. 102(e) as being clearly anticipated by Popescu et al. (US 5,897,873).

The claims are drawn to a complex comprising a negatively charged adjuvant electrostatically associated with a positively charged antigen to induce a CTL response. The adjuvant specifically comprises lipid A.

Popescu et al. clearly anticipate an immune complex comprising lipid A comprising phosphatidic acid or phosphatidyl glycerol that is electrostatically associated with a positively-

charged antigen, see column 3, line 65 to column 5, line 5 and lines 35-37, column 8, lines 11-15 and claims 1-8. This complex of Popescu et al. also induces a CTL response, see column 2, lines 5-16.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-11 and 17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cox et al. (Vaccine. 1997; 15 (3): 428-256) and Callahan et al. (Pharmaceutical Research. 1991; 8 (7): 851-858).

The claims are drawn to a complex comprising a negatively-charged adjuvant and a positively-charged antigen, where the adjuvant is ISCOMATRIX™.

Cox et al. review adjuvants and more specifically ISCOM™ complexes on page 251 and teach that these complexes induce Th1 and Th2 responses against antigens incorporated into them. Cox et al. do not teach the electrostatic association between the antigen and the ISCOM™.

However, Callahan et al. teach the importance of surface charge in antigen-adjuvant complexes and clearly demonstrates that there is enhanced adsorption between a positively charged antigen and a negatively charged adjuvant, see the entire reference.

One of ordinary skill in the art at the time the invention was made would have been motivated to incorporate positively charged antigens and negatively-charged adjuvants to

increase antigen adsorption into the adjuvant carrier matrix. One of ordinary skill in the art at the time the invention was made would have also been motivated to augment the complementary isoelectric charges of each antigen/adjuvant component to increase antigen incorporation into the adjuvant. One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation for increasing adsorption of positively-charged antigens into ISCOMs because both reference teach that the respective adjuvants incorporate antigens into the matrix. Therefore, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made, absent unexpected results to the contrary.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-17 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-32 of copending Application No. 09/714438 for reasons of record.

Applicant states that this rejection will be officially addressed upon notification of allowable subject matter. Applicant's statement is noted and until such time, this rejection is maintained.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shanon Foley whose telephone number is (703) 308-3983. The examiner can normally be reached on M-F 9:00-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel can be reached on (703) 308-4027. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4426 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Shanon Foley
February 20, 2003

JAMES HOUSEL 2/23/03
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600